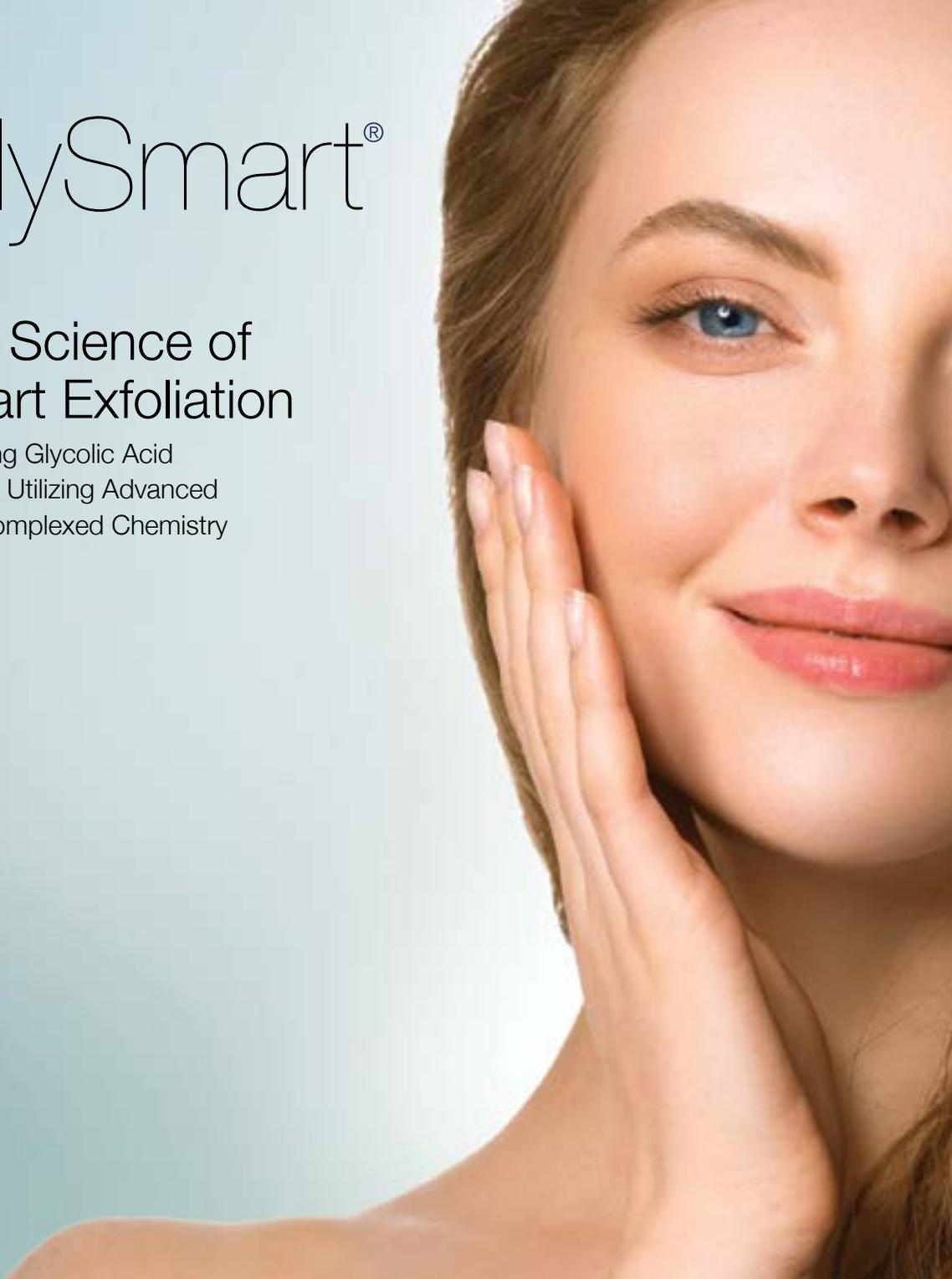


GlySmart[®]

The Science of Smart Exfoliation

Reducing Glycolic Acid
Irritation Utilizing Advanced
Ionic-Complexed Chemistry



Introduction

Through chemical exfoliation treatments, damaged outer layers of the skin are removed and newer, healthier skin cells beneath are exposed. In particular, glycolic acid, known for its small size and molecular stability, is a naturally-occurring α -hydroxy acid. Often used as an active ingredient in skin care formulations, the effectiveness of glycolic acid in driving skin exfoliation is widely recognized. Glycolic acid's strength, however, can lead to instances of irritation when used by those with more delicate skin surfaces. Variations in skin sensitivity and pH tolerance between individuals means that the same chemical reactions between glycolic acid and the skin surface can cause irritation and lead to discomfort in some while being acceptable for others. Because of this, a new solution has arrived that controls the release of glycolic acid onto the skin surface and prevents skin discomfort.

The following research and testing will describe and validate CrossChem's solution: GlySmart[®], a new glycolic acid-based molecular ionic complex. Taking advantage of CrossChem's formaldehyde-free GlyAcid[®], ideal in personal care, the GlySmart[®] product is a new, more finely attuned exfoliation solution. Designed to effectively exfoliate the skin as the original GlyAcid[®] product, GlySmart[®] uses an amphoteric molecule to moderate the release of glycolic acid onto the skin surface and prevent the skin discomfort associated with glycolic acid exfoliators.

Key Areas of Study

This research validates previous studies addressing increased skin sensitivities with glycolic acid skin care products. Specifically we address:

- Potential causes of skin irritation with glycolic acid based skin exfoliation
- How elevated skin pH, typically among women, can increase irritation and redness
- Reducing irritation by slowing the release of glycolic acid through an amphoteric complex



Figure 1
Cellular Replenishment

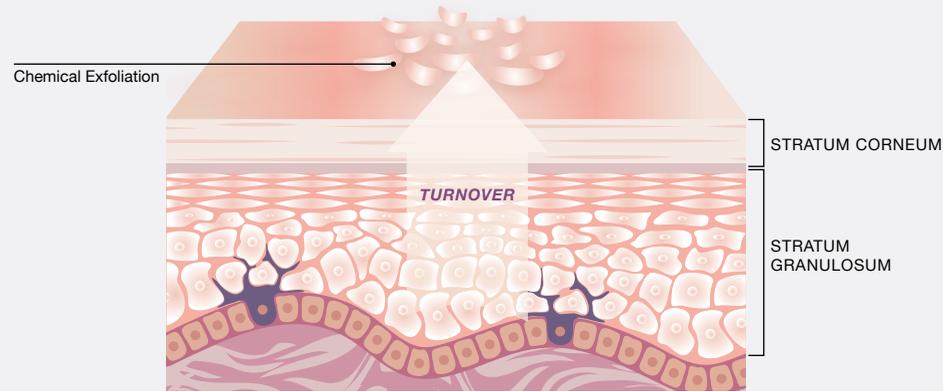
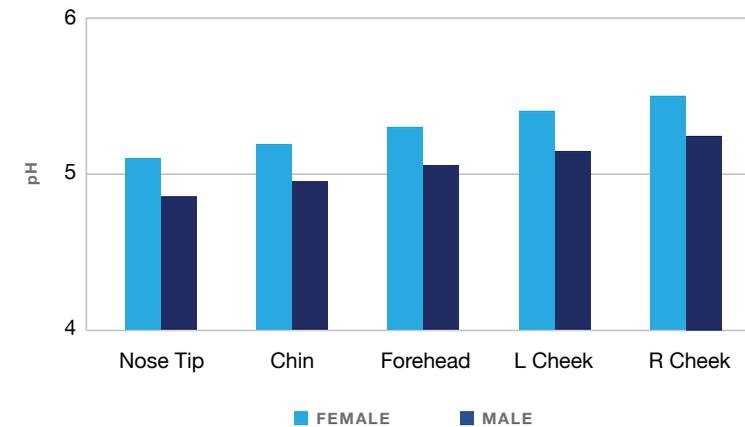


Figure 2
pH Differences
Male vs. Female



Cellular Replenishment Challenges

Higher pH of Women's Skin

The restoration and repair of the outer layers of the skin has long been a key component of skin-aging therapies. The outermost skin layer, the stratum corneum, works to shield the rest of the skin. Nevertheless, the cells of the stratum corneum are constantly faced with environmental damage that can stress and disrupt the structure of the stratum corneum layer, leading to skin aging. As such, treating the health of the stratum corneum is crucial to effective anti-aging solutions. Exfoliators, products applied to the outer layers of skin that cause it to peel off, expose healthier new skin cells beneath and have long been a key tool in

spurring cellular rejuvenation. Therapeutics based on exfoliation can alleviate cosmetic blemishes and symptoms of dermatologic conditions. The resulting new, exfoliated skin is usually smoother, healthier, and less wrinkled than the previous stratum corneum layers.

Chemical exfoliators are a decisive and beneficial tool in skin therapy. They are particularly useful as they can improve skin health and appearance while avoiding the need to manually remove skin cells through mechanical exfoliation and other physical treatments. Particularly, treatment with acidic skin exfoliators like glycolic acid are effective in jump-starting the generation of new skin cells.

Glycolic acid is a celebrated natural, active ingredient in skin care, used in a wide variety of skin exfoliating formulations. Glycolic acid is the smallest and simplest of the α -hydroxy acids and is highly effective in penetrating between cells on the skin surface and chemically exfoliating the stratum corneum layer. When topically applied, α -hydroxy acids jump-start cellular replenishment, bringing newly formed, healthy layers of cells to the surface of the SC (**Figure 1**).

The molecular interactions that make chemical exfoliation so successful, however, can also lead to skin irritation as these products work to accomplish their goal. The pH of the skin is crucial to health and plays a meaningful role in maintaining homeostasis and immune functions [3]. Research has shown that the natural pH of the skin surface varies not only between the sexes, but between individuals [1].

Because of this, the same acidic chemical exfoliator might cause minimal discomfort when applied to one subject's skin, while causing measurable irritation when applied to someone else. The surface pH of human skin is typically slightly acidic, generally with a pH around 4.7 to 5 [2]. The pH of skin can be affected through the use of shampoos, cleansers, or even simple tap water, which in many cases are basic (with pH values above 7) and can shift the pH of the skin surface [2]. These environmental shifts in skin pH can affect the behavior of skincare products when applied to the skin. This is especially important in consideration of data that shows the surface of women's skin is generally more basic (tends to have a higher pH) than that of men. A study published in the Journal of Dermatological Science noted that recorded pH values of women's skin samples had a pH approximately 0.25 higher than corresponding samples from men [2] (**Figure 2**).

Figure 3
Arginine



Due to higher pH values across the board, women's skin will behave differently and potentially be more sensitive when exposed to acidic compounds as compared to men's skin.

Acidic chemical exfoliators work through acid-base reactions when applied to the skin, which spur the peeling of the stratum corneum and its replacement with new, healthy cells. In general, the greater the pH difference between the acidic formulation and the skin, the more intense the reaction will be. When the skin surface becomes more basic, the potential reaction between an acid exfoliator and the skin becomes stronger and more rapid. However, this stronger reaction can also lead to greater irritation to the skin, causing sensitivity, redness, and stinging during the treatment process. The greater basicity of women's skin means that a one-size-fits-all skincare product might cause serious irritation for women while being less irritating for men. With individual skin

characteristics in mind, a smarter solution is needed that can moderate the irritating effects of chemical exfoliation, promote gentle healing, while at the same time take advantage of the uniquely powerful and effective solution offered by glycolic acid in skincare.

CrossChem's solution is GlySmart®, a molecular complex of glycolic acid and arginine, a natural amino acid with important roles in healing and immune function [4] (Figure 3). The GlySmart® molecule uses proven science to create a skincare solution that combines the effectiveness of a pure glycolic acid formulation with a gentleness to minimize skin irritation during use. The principle at the heart of GlySmart® is the formation of a new molecular complex when glycolic acid and arginine bond together.

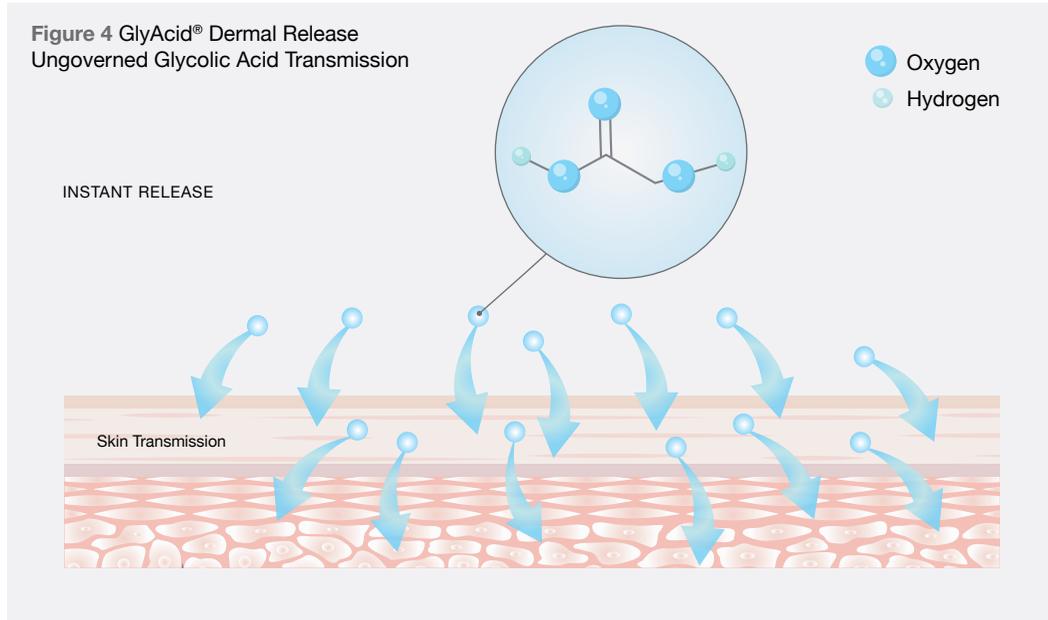


This idea was first described by Ruey J. Yu and Eugene J. Van Scott in 1992 in Amphoteric Compositions and Polymeric Forms of Alpha Hydroxyacids, and Their Therapeutic Use [5]. In their patent, US5091171, Yu and Van Scott describe that α -hydroxy acids, while an effective skincare therapeutic, "may irritate human skin on repeated topical applications due to lower pH of the formulations" [5]. Their solution was to create a new amphoteric molecule to work alongside the α -hydroxy acid. An amphoteric molecule is a molecule that can behave like an acid or a base, depending on the circumstances. In this case, this new amphoteric molecule raises the pH of the overall

formulation, decreasing the potential for skin irritation. The new molecule likewise interacts with the original α -hydroxy acid to form a "quadruple ionic complex" which governs the release of the α -hydroxy acid into the skin, reducing skin irritation while retaining effectiveness [5].

More recent work by BASF has further clarified the science behind the amphoteric α -hydroxy acid solution. BASF harnessed arginine to work in conjunction with glycolic acid to create a compound that, when applied to the skin, conveys the benefits of glycolic acid while avoiding skin irritation. Tests conducted by

Figure 4 GlyAcid® Dermal Release
Ungoverned Glycolic Acid Transmission



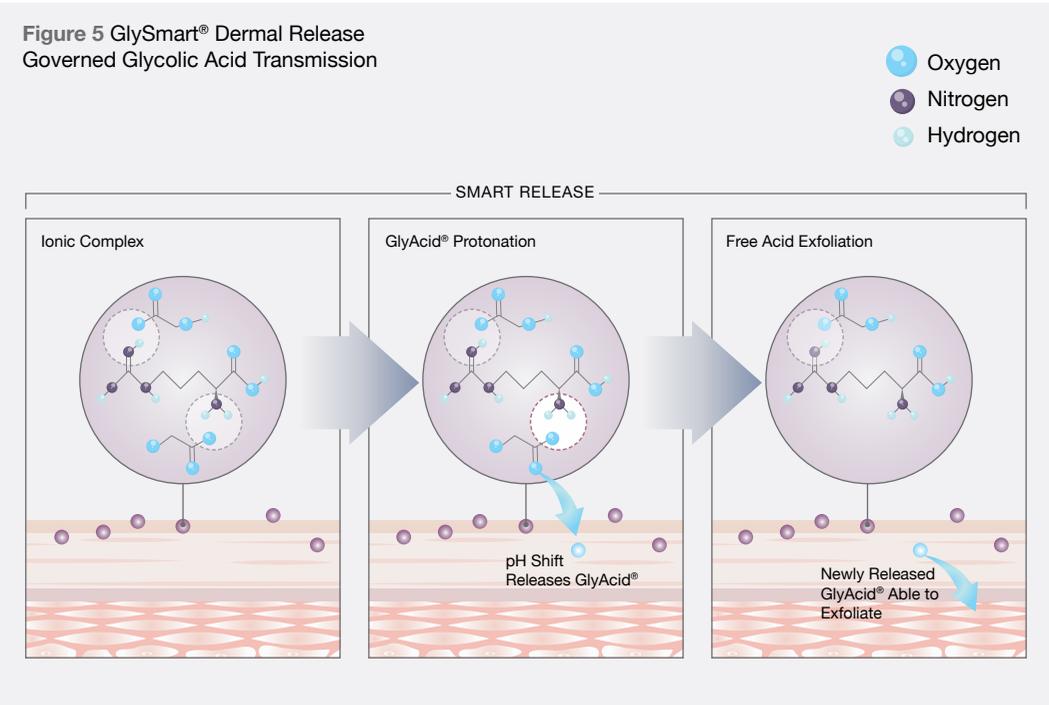
BASF have shown that treatment with arginine α -hydroxy acid compounds increase cellular turnover at a similar rate to treatment with pure α -hydroxy acid formulations, showing similar effectiveness in skin exfoliation. Conversely, sting study results from BASF have shown that application of the amphoteric formulation significantly decreases the discomfort and irritation experienced by subjects during treatment.

The Science of an Amphoteric Complex

To understand why GlySmart® is an ideal remedy for irritation arising during exfoliation, it is important to understand the science behind the GlySmart® concept. When a formulation composed solely of an α -hydroxy acid like glycolic acid is applied to the skin, there are no

restraints on the ability of the α -hydroxy acid to bond with and into the skin surface (Figure 4). As the α -hydroxy acid enters the skin, beginning the exfoliation process, the large-scale replacement of the outermost skin layers all at once can create the types of irritation that may make exfoliation uncomfortable for those with more sensitive skin. However, the addition of a new amphoteric molecule can instead modulate the interactions between the α -hydroxy acid and the skin, controlling the reaction and minimizing the potential for irritation. In GlySmart®, glycolic acid and arginine form a complex with two acid-base pairs (dipoles), creating the quadruple ionic complex. Arginine is an amino acid, a class of organic molecules mainly composed of nitrogen, carbon, hydrogen, and oxygen [6]. Amino acids possess a carboxylic acid on one end and an amine group on the other end, with a variable side

Figure 5 GlySmart® Dermal Release
Governed Glycolic Acid Transmission



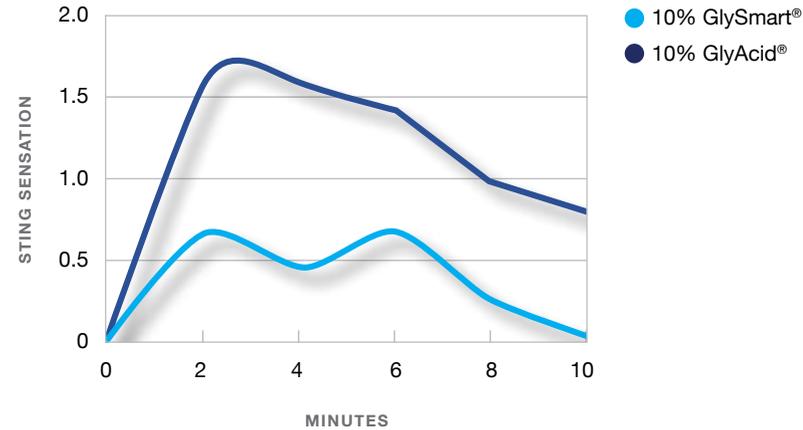
chain in the middle. The unique side chains on each amino acid differentiates them and gives each one different properties [6].

Arginine is especially useful amongst the amino acids because it possesses a guanidino group in addition to the amino group, and it can react with glycolic acid under neutral conditions. In this case, arginine makes glycolic acid slightly more basic to make it less irritating. Furthermore, under slightly acidic conditions like those found on the skin surface, the new amphoteric complex would release low concentrations of glycolic acid over time, allowing glycolic acid to interact with the skin in a controlled, moderate manner.

CrossChem's GlySmart® solution is the newest improvement to this natural and effective strategy. Building upon the science behind previously existing amphoteric α -hydroxy acid products, GlySmart® employs CrossChem's GlyAcid®, a globally leading high purity glycolic acid to create a next-level product for skincare use. Application of GlySmart® allows for a bridled release of glycolic acid onto the skin, where the arginine-glycolic acid complex will respond to the pH of the skin surface by releasing the glycolic acid molecules a bit at a time, delivering the same end-result exfoliation over a more sustained duration while avoiding irritation caused by overloading the skin with glycolic acid (Figure 5). As previously mentioned, glycolic acid is unmatched as a

Figure 6
Mean Sensitivity Validation*
57% – 80% Less Sensation

*CrossChem In-House Data



personal care ingredient due to its simplicity and small molecular size.

Glycolic acid has been proven to be highly effective in penetrating the skin surface, leading to more effective skin exfoliation. GlyAcid® is a formaldehyde-free and high purity glycolic acid designed and engineered for personal care formulations. Anchoring GlySmart® with GlyAcid® provides the best of both worlds, combining the power of glycolic acid in personal care with enhanced sensitivity, while matching other formulations in effectiveness and comfort.

Proven Effectiveness

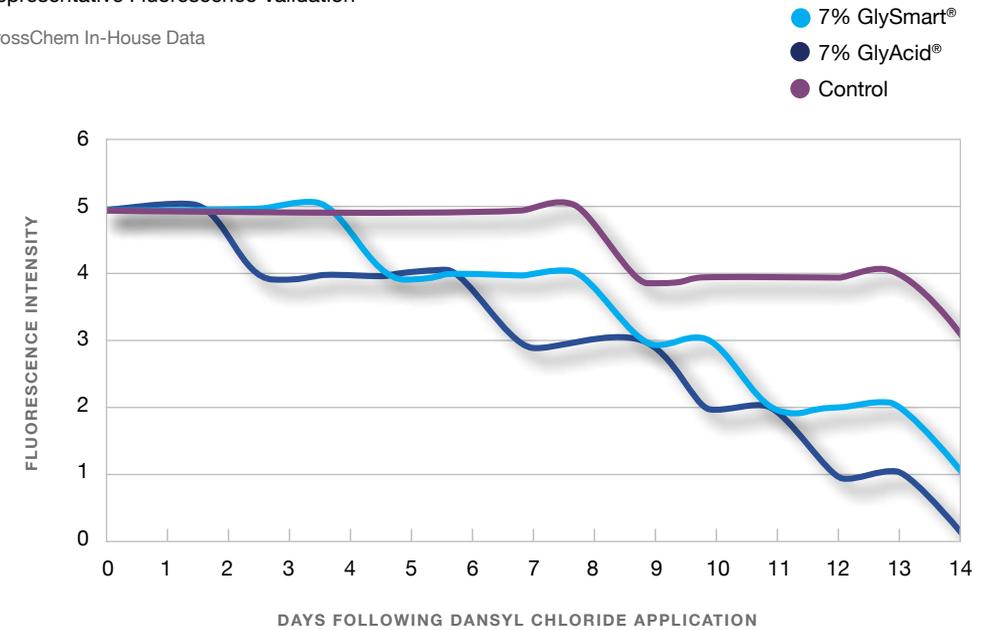
Trials of GlySmart® have proven its effectiveness in fulfilling personal care requirements while at the same time preventing skin irrita-

tion. Testing conducted by CrossChem analyzed both cellular turnover and skin irritation during use of the GlySmart® compound, validating GlySmart® through comparisons to prior clinical studies. Sting testing demonstrated decreased levels of discomfort after use of the amphoteric glycolic acid solution as compared to a glycolic acid aqueous solution (Figure 6).

Fluorescence measurements of cellular turnover likewise showed thorough exfoliation of the stratum corneum on timescales comparable to that of the purely acidic solution, confirming that GlySmart® can just as effectively exfoliate the skin as a normal α -hydroxy acid can (Figure 7). Overall these tests validate the efficacy of GlySmart® while being consistent with previous studies observed.

Figure 7
Representative Fluorescence Validation*

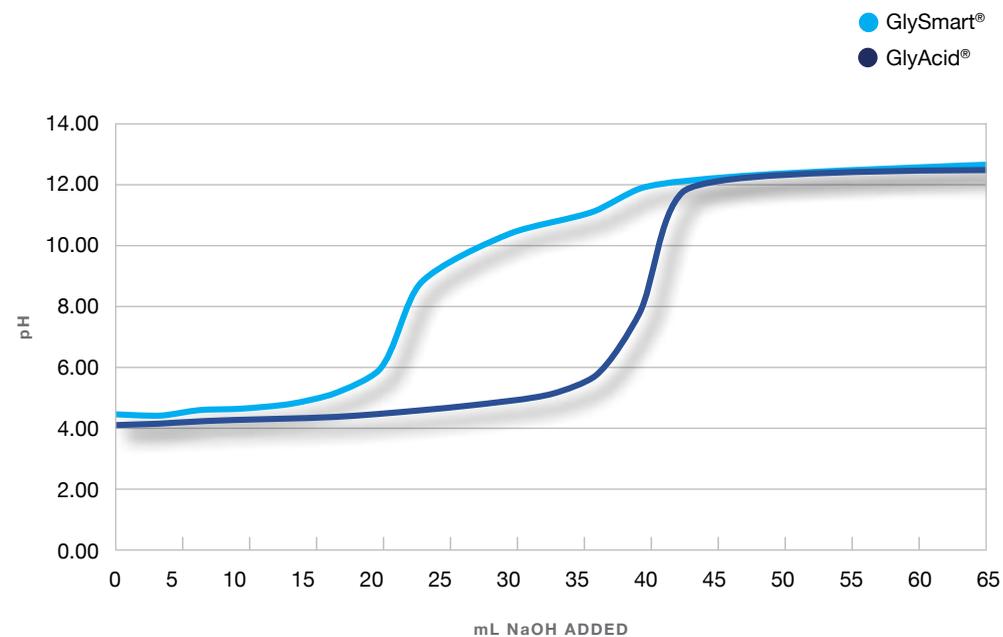
*CrossChem In-House Data



Additionally, titration testing was conducted to measure the difference in pH change over time between a 1.0 M glycolic acid solution and a 1.0 M glycolic acid/arginine solution. In this test, both samples were titrated with sodium hydroxide (NaOH) to measure shifts in pH. As seen in Figure 8, the test results demonstrated that under the same conditions, the amphoteric glycolic acid/arginine compound was less prone to rapid shifts in pH. The addition of basic NaOH to both samples showed the GlySmart® sample to be much more resistant to sudden pH change, demonstrating a slower, steadier increase in pH as compared to the GlyAcid® solution.

The data shows that in the test, it took only 3 mL of NaOH base to move the pH of the GlyAcid® solution from a pH of approximately 5.3 to a pH of approximately 12. In the same test, it took the addition of 8 mL of NaOH to shift the pH of the GlySmart® sample the same amount. In application, the behavior seen in these tests would allow for the controlled release of glycolic acid into the skin over time, regardless of variations in pH of the skin surface.

Figure 8 Titration Curve
GlySmart® vs. GlyAcid®



Likewise, the more stable slope as seen in **Figure 8** is indicative of only some of the glycolic acid in the solution being released over time. In instances of higher basicity, such as on the female skin surface as described above, treatment with GlySmart® prevents the more extreme acid-base reactions that would other-

wise occur. This modulated release of glycolic acid from the quadruple ionic complex is central to GlySmart®'s more sensitive approach to skin irritation, and shows that even in more basic conditions, GlySmart® can prevent the uncontrolled release of glycolic acid and the skin irritation that can accompany it.

Conclusion

Glycolic acid, with its small size and relative molecular stability, has commonly been used as an active ingredient in skin care formulations within the personal care industry. While α -hydroxy acids, and especially glycolic acid, are well-known and appreciated naturally

occurring exfoliators, the chemical reactions between glycolic acid and the skin surface can cause irritation and lead to discomfort as they bond into the outer layers of the skin and lead to peeling of the stratum corneum.



With GlySmart®, however, a complex between glycolic acid and a new amphoteric molecule leads to a new, more finely attuned exfoliation solution. Taking advantage of the purity of CrossChem's formaldehyde-free GlyAcid®, the ideal for personal care, the new GlySmart® product combines arginine with GlyAcid® to create a powerful amphoteric formulation.

Designed to just as effectively exfoliate the skin as the original GlyAcid® product, GlySmart® uses arginine to moderate the release of glycolic acid onto the skin surface and prevent skin discomfort. Studies have shown that the arginine-glycolic acid formulation is similarly

effective to glycolic acid alone in spurring skin replenishment. Testing has also shown GlySmart® to be successful in controlling exfoliation and preventing rapid changes in pH during application, while at the same time minimizing irritation for those with sensitive skin.

With the advent of GlySmart®, a smarter approach to skin rejuvenation is available for those with more sensitive skin, providing gentleness in skin exfoliation without compromising effectiveness. This study validates the existing evidence that GlySmart® is a key component in next generation skincare therapeutics.

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CROSSCHEM LIMITED | 100 WESTWOOD PLACE STE 430 | BRENTWOOD TN 37027 USA | +1 615 716 3510

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